FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OPHTHALMIC DEVICES PANEL

107TH MEETING

THURSDAY,
FEBRUARY 5, 2004

The Panel met at 9:00 a.m. in Salons B-D of the Gaithersburg Marriott Washingtonian Center, 9751 Washingtonian Boulevard, Gaithersburg, Maryland, Jayne S. Weiss, M.D., Chair, presiding.

PRESENT:
JAYNE S. WEISS, M.D., Chair
ARTHUR BRADLEY, Ph.D., Voting Member
ANNE L. COLEMAN, M.D., Ph.D., Voting Member
MICHAEL R. GRIMMETT, M.D., Voting Member
WILLIAM D. MATHERS, M.D., Voting Member
TIMOTHY T. McMAHON, O.D., F.A.A.O., Voting Member
KAREN BANDEEN-ROCHE, Ph.D., Consultant
RICHARD CASEY, M.D., Consultant
ANDREW J. HUANG, M.D., M.P.H., Consultant
MARIAN S. MACSAI-KAPLAN, M.D., Consultant
OLIVER D. SCHEIN, M.D., M.P.H., Consultant
JANINE A. SMITH, M.D., Consultant
WOODFORD S. VAN METER, M.D., Consultant
GLENDA V. SUCH, M.Ed., Consumer Representative
ANDREW K. BALO, Acting Industry Representative
SARA M. THORNTON, Executive Secretary

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JEFFREY TOY, Ph.D.
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RICK McCARLEY
STAN BENTOW, Ph.D.
R. DOYLE STULTING, M.D., Ph.D
VANCE THOMPSON, M.D.

A-G-E-N-D-A

COMMITTEE DELIBERATIONS

OPEN MEETING ADJOURNED

P-R-O-C-E-E-D-I-N-G-S

9:01 a.m.

DR. WEISS: I'm going to ask everyone to take their seat, please. We'll be starting shortly. I would like to call this meeting of the Ophthalmic Devices Panel to order and note that there is a quorum present. We will have introductory remarks by Sally Thornton.

MS. THORNTON: Good morning. Permit me to introduce myself. I'm Sara Thornton, Executive Secretary for the panel. On behalf of the FDA I would like to welcome you to the 107th meeting of the Ophthalmic Devices Panel.

Before we proceed with today's agenda, I have a few short announcements to make. First of all, I would like to remind everyone to please sign in on the attendance sheet on the registration area just outside the meeting room here. All public handouts for today's meeting are available at the registration table.

Messages for panel members and FDA participants, information, or special needs should be

directed through Ms. AnnMarie Williams who is available at the registration area. The phone number for calls to the meeting area is (301) 590-0044.

In consideration of the panel, the sponsor and the Agency, we ask that those of you with cell phones and pagers either turn them off or put them on vibration mode while in this room and to make your calls, please, outside the meeting area. Note the flyers on the door.

Lastly, will all meeting participants please speak directly into the microphone and give your name clearly so that the transcriber will have an accurate recording of your comments.

Now, at this time I would like to announce the voting member appointment of Dr. William Mathers of the Casey Eye Institute in Portland, Oregon. Dr. Mathers has been appointed to serve until October 31st of 2007.

I would like to welcome our Acting Industry Representative, Mr. Andrew Balo, Vice President for Regulatory and Clinical Affairs with DEXCOM, Inc. in San Diego, California. Mr. Balo also

serves as the Industry Representative on the Neurological Devices Panel. Mr. Balo is sitting in for our panel Industry Representative Mr. Ronald McCarley who has recused himself from today's panel deliberations.

Will the remaining panel members please introduce themselves beginning with Glenda.

MS. SUCH: Glenda Such, Lighthouse International, Consumer Representative.

MR. BALO: Andy Balo, Industry Representative.

DR. SCHEIN: Oliver Schein, Wilmer Eye Institute, Johns Hopkins.

DR. BANDEEN-ROCHE: Karen Bandeen-Roche, Department of Biostatistics, Johns Hopkins.

DR. McMAHON: Timothy McMahon, Department of Ophthalmology, University of Illinois at Chicago.

DR. BRADLEY: Arthur Bradley, School of Optometry, Indiana University.

DR. MACSAI: Marian Macsai, Evanston Northwestern Healthcare, Northwestern University.

DR. GRIMMETT: Michael Grimmett, the

Bascom Palmer Eye Institute, the University of Miami.

DR. WEISS: Jayne Weiss, Kresge Eye Institute, Wayne State University School of Medicine.

DR. MATHERS: Bill Mathers, Oregon Health Sciences University.

DR. CASEY: Richard Casey, Charles Drew University, Jules Stein Eye Institute, Los Angeles.

DR. COLEMAN: Anne Coleman, Jules Stein Eye Institute, UCLA.

DR. VAN METER: Woody Van Meter, the University of Kentucky in Lexington.

DR. HUANG: Andrew Huang, University of Minnesota.

DR. ROSENTHAL: Ralph Rosenthal, Division of Ophthalmic and ENT Devices, FDA.

MS. THORNTON: I'd like to just announce that Dr. Janine Smith who will be in attendance at the panel will be here in a very short time.

I'd like to now read the conflict of interest statement for the meeting on February 5, 2004. The following announcement addresses conflict of interest issues associated with this meeting and is

made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the Agency reviewed the submitted agenda for this meeting and all financial interest reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matter that could affect their or their employer's financial interest.

The Agency has determined, however, that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government. Therefore, waivers have been granted for Drs. Michael Grimmett, Oliver Schein, and Woodford Van Meter for their interest in firms that could potentially be affected by the panel's recommendations.

Dr. Grimmett's waiver involves an imputed interest, a grant to his institution for the sponsor study in which he has no involvement and is uncompensated. Dr. Oliver Schein's waiver involves

two consulting arrangements, one pending for a competitor's unrelated device for which he has not received any compensation, and the second with a competitor's unrelated device for which he receives an annual fee between $10,000 and $50,000. Dr. Van Meter's waiver involves an imputed interest, a stockholding in the parent of a competing technology firm in which the value is greater than $100,000.

The waivers allow these individuals to participate fully in today's deliberations. Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A15 of the Parklawn Building. We would like to note for the record that the Agency took into consideration other matters regarding Drs. Anne Coleman, Arthur Bradley, Michael Grimmett, Andrew Huang, Marian Macsai, Oliver Schein, and Jayne Weiss.

Each of these panelists reported past or current interest involving firms at issue but in matters that are not related to today's agenda. The Agency has determined, therefore, that the panelists may participate fully in all discussions.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

I would like to now read the appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990, and as amended August 18, 1999, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for this meeting on February 5/6, 2004.

Karen Bandeen-Roche, Ph.D., Richard Casey, M.D., Marian S. Macsai-Kaplan, M.D., Oliver Schein, M.D., Andrew Huang, M.D., Janine Smith, M.D., Woodward Van Meter, M.D.

For the record, these individuals are special government employees and consultants to this panel or other panels under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. Signed, David W. Feigal, Jr., M.D., MPH, Director, Center for Devices and Radiological Health. Dated January 20, 2004.

Thank you, Dr. Weiss.

DR. WEISS: Thank you, Sally.

We will now open the open public hearing. I will read a statement which was requested by the FDA.

"Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency of the open public hearing session of the Advisory Committee, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you,

the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking."

I would call Glenn Hagele to the podium as the first public speaker. You have up to 10 minutes.

MR. HAGELE: I need some assistance with the video. Dr. Weiss, with your permission, could I come after the following speaker?

DR. WEISS: Why don't you stay up there if they can arrange that, Mr. Hagele, because we have a

written letter from someone and perhaps we can use this window of time to read the letter while you're preparing your --

MR. HAGELE: Thank you.

DR. WEISS: If that would be agreeable.

Sally Thornton has a letter that was sent in from someone who wanted to participate in the open public hearing but was not able to appear.

MS. THORNTON: This is a letter from Peter D. Van Patten, M.D., the Duluth Clinic Virginia in Virginia, Minnesota.

"Dear Ms. Thornton. I had planned to make a short presentation at today's meeting but could not attend due to a scheduling conflict. If possible I would like to have my following comments read into the record during the appropriate time slot of the meeting.

My name is Peter D. Van Patten. I have practiced ophthalmology since 1991. I am also a subject in the U.S. clinical study of the ARTISAN Myopia Lens and have bilateral ARTISAN implants. I have no financial interest in the ARTISAN lens or

Ophtec, the sponsor of this study.

The purpose of my testimony is to provide additional information to the FDA and the FDA panel for consideration during today's discussions. Prior to receiving ARTISAN lenses my refractions were -10.0 X -0.75 in both eyes. Previously I was having increasing problems with contact lens wear to the point where the symptoms became intolerable.

After considering all available options, I decided to proceed with the ARTISAN lens implant. My left eye received the ARTISAN lens in February '99, five years ago, and my right eye received the lens in March 2001, nearly three years ago.

My current refractions are -0.75 X -0.5 in the left eye and plano X -0.5 in the right eye. I have an uncorrected acuity of 20/30 in the left eye correctable to 20/20 and 20/20 uncorrected vision in the right eye correctable to 20/15. My outcomes were very successful and my overall vision is excellent.

I typically wear glasses only for night driving. I have experienced mild night glare on occasion postoperatively that was not present prior to

receiving the lenses. However, I would rate the level of glare as minimal.

I have had significant functional improvements during my high visual demand activities such as ophthalmic surgery. Also, I would rate my daytime vision as suburb. I consider both procedures to be a success. Over the past five years I have continued to discuss the ARTISAN lens as an important investigational surgical option with my patients whom I found to be appropriate candidates for open ARTISAN lens clinical trials.

Based on my experience as a subject in this study, it is my opinion that the ARTISAN lens is a safe and effective lens when implants by a skilled surgeon. I would ask that you consider my comments during your discussions and hope that you are able to make a favorable recommendation today so as to make this technology available to others who seek correction for high myopia. Sincerely, Peter D. Van Patten, M.D."

DR. WEISS: Thank you, Sally.

Mr. Hagele, are you ready?

MR. HAGELE: We are coming up momentarily.

DR. WEISS: Sounds good. If you're still having difficulty, I understand that Ms. Woodlock does not have slides so she perhaps could do her presentation while you are getting that ready.

MR. HAGELE: Thank you.

DR. WEISS: Ms. Woodlock. Would you mind, perhaps, giving your presentation from the table instead? Thank you.

MS. WOODLOCK: I am Leslie Woodlock, Patient Advocate of the Surgical Eyes Foundation. We are a nonprofit organization whose constituency is consumers with sub-optimal outcomes from refractive surgery. Our goals are simply to raise awareness of the risks of elective eye surgery, provide support and identify solutions for patients living with complications, and advocate for informed decision making. I personally became involved with the Surgical Eyes Foundation after failed LASIK surgery in 2000.

I am here today to discuss the safety of phakic lOLs. While much of SEF's concern with the ICL was discussed at this panel's meeting on October 3,

2003, we would like the panel to address the following issues:

Diameter selection is critical for centration of this device since under sizing could result in a failure of the lens to vault the anterior capsule properly, resulting in contact of the device with the capsule and subsequent anterior cortical cataract development.

The need for a tight fit is recognized by the applicant and yet selection of the ICL diameter is to be based on the white-to-white measurement. Since no exacting correlation between the white-to-white measurement and the ciliary sulcus diameter exists, how will patients be protected from secondary cataract development?

The increasing thickness of the physiologic lens with aging as well as during accommodation means that the desired post-operative vault of the ICL will fluctuate and actually diminish over time. This has the potential to accelerate the development of anterior cortical cataracts.

The incidence of endothelial cell loss is

a repeated concern throughout the previous discussion. In the event that the ICL must be removed following a noted progression of anterior capsular opacities, there is no evidence suggesting that explantation of the ICL will be less harmful to the endothelium than its continued presence.

Further, in cases of either device-induced or naturally occurring cataracts, the ICL will have to be explanted before the implantation of a pseudophakic IOL. Clearly, for all patients, a second and possibly third intraocular procedure must be entertained with further potential for loss of endothelial cells.

Continuing with our concern for loss of a functional endothelium, the dynamics of a shallow anterior chamber depth and progressive endothelial cell loss is unknown at this time. Most cases of Fuchs' endothelial dystrophy do not become clinically evident until patients are approaching their fifth decade. Will implantation of the ICL result in an even earlier loss of endothelial integrity and, ultimately, penetrating keratoplasty?

These patients would appear to be at even

higher risk for endothelial cell loss regardless of an allowable standard for minimal anterior chamber depth of 2.8 or 3 mm. It is not possible to assess risk for younger individuals at the time the ICL is implanted since they will not have visible indications for the condition.

Revisiting the effects of aging of the physiologic lens, another consequence is the shallowing of anterior chamber. The applicant has found a correlation of shallow anterior chamber depth to endothelial cell loss. It is reasonable to suspect that aging of the crystalline lens and subsequent reduction of the anterior chamber depth will put older patients at increased risk for decompensation of their corneas secondary to endothelial dystrophy.

In regard to implantation of this device, typically the risk of cystoid macular edema increases with each intraocular surgical procedure. In the case of device-induced cataracts with subsequent explantation followed by implantation of a pseudophakic IOL, the potential for CME would be significantly greater.

Correct positioning of the ICL requires a tight sulcus to sulcus fit with anterior displacement of the iris. The fact that the potential narrowing of the anterior chamber angles following implantation was not consistently examined via gonioscopy in the PMA suggests only a cursory concern with the potential for narrow angle glaucoma. Patients with naturally narrow anterior chamber angles as well as those whose angles will narrow subsequent to aging, are at higher risk for development of glaucoma.

The presence of the ICL vaulting above the anterior capsule changes the dynamic of the posterior iris and its contact with the anterior capsule. The potential for pigment dispersion is very real as the ICL haptics rub against the posterior iris.

Pigment dispersion has a known occurrence in the general population but does not manifest until the fifth decade. Implantation of this device in younger patients with a predilection for pigment dispersion will quite conceivably accelerate the process and lead to pigmentary glaucoma.

Anterior cortical cataracts, narrow angle

glaucoma, pigmentary glaucoma and endothelial dystrophy are naturally occurring conditions but are potential complications of the ICL. A very real possibility exists that health insurers will not cover the cost of treatment for these conditions since they could be viewed as secondary to an elective procedure.

SEF is already aware of patients receiving corneal transplants following corneal refractive surgery who were denied reimbursement by their health insurer for this very reason. The negative impact on the patient is two fold. Either they will be denied coverage for a naturally occurring medical condition or they will have to pay for the deniable complications secondary to an elective surgery.

The optical diameter of the ICL is listed as 4.65 to 5.5 mm. While the diameter of a posterior chamber ICL cannot be compared to the typical, stated ablation diameters of LASIK and PRK, it is interesting that the optical diameter is so small. Pseudophakic lOLs are typically in the 6.0 mm range and there are still patients who will notice glare and halos under low light conditions.

Using our knowledge of pseudophakics' experience as a guide and, given that the population having ICL surgery would typically be much younger with larger pupils, it would seem very certain that many individuals will experience unwanted glare and haloes from spherical aberrations created by the uncorrected rays of light passing through the peripheral physiologic lens.

Continuing on with the discussion of the optical diameter effects, it is necessary to mention the recent publication of Dr. Steven C. Schallhorn's study suggesting the irrelevance of pupil size to visual quality under mesopic and scotopic light conditions, in particular, that pupil size does not correlate with night driving performance.

This oft touted study, however, does nothing to explain why numerous journal articles by leading refractive surgeons suggest the use of brimonidine tartrate (Alphagan), an adrenergic agonist that suppresses pupil dilation to produce a relative miosis, as well the direct-acting miotic, pilocarpine, be used post-operatively to suppress the ill-effects

of night time driving in refractive surgery patients.

The Surgical Eyes Foundation bulletin board is overflowing with empirical evidence from our patients and our participating doctors of the effectiveness of pupil constricting agents in the reduction of low light glare and halos. Our bulletin board already has one ICL patient complaining of this very thing and two well-known refractive surgeons recommended Alphagan as the remedy.

With regard to quality of vision, we ask that PMAs for all forms of vision correction devices be stratified by pupil size. The PDA should mandate that quality of vision be measured objectively with wavefront and other objective tests that have been utilized by optical scientists like Dr. Raymond Applegate that stratify results by pupil size, and that these results be published and made readily available to consumers with regard to any form of vision correction device.

We have had many patients of all ages with large pupils post on our bulletin board about nighttime visual aberrations, regardless of refractive

error. We understand that an effective optical zone on the corneal surface and the optic diameter of a lens that sits behind the iris are not comparable; however, we feel very strongly that patients with large pupils are at risk with this device.

One common experience of patients visiting our web site and bulletin board is in regards to the informed consent agreement. While explanations of potential visual and physiological complications are discussed, patients typically do not understand the chronic and irreversible nature of those complications.

Informed consent continues to be a major concern of SEF for elective refractive surgery. Unnatural visual effects seem to impact deeply on many patients sense of well being. The psychological emotional aspects of vision complications are not something potential patients can understand or be prepared to accept following negative outcomes.

This completes my presentation. On behalf of the board of trustees of the Surgical Eyes Foundation and our constituency, I wish to thank the

Advisory Panel for the opportunity to express our concerns. Thank you very much.

DR. WEISS: Thank you very much.

And you will be limited to 10 minutes for your presentation.

MR. HAGELE: That should be more than adequate. Good morning and thank you for the opportunity to address this panel. My name is Glenn Hagele. I am the Executive Director and founder of the Council for Refractive Surgery Quality Assurance, which from this point forward I will refer to by its acronym CRSQA.

In the way of disclaimer, I have no financial interest in AMO or the ARTISAN phakic intraocular lens. My travel here today is self-funded. Although I am the Executive Director of CRSQA, the opinions I express are my own and do not necessarily represent the opinions of individuals affiliated with CRSQA.

CRSQA is a nonprofit consumer/patient organization that through its sister websites USAeyes.org and ComplicatedEyes.org receives over

800,000 visitors annually. We provide objective information about refractive surgery issues and resources for those unfortunate few who have encountered a poor refractive surgery outcome.

Additionally, CRSQA evaluates and certifies refractive surgeons based upon patient outcomes. In addition to research of published studies and case reports, my interaction with patients provides me with a unique accumulation of anecdotal information and a perspective of a patient. The issues and concerns I will raise today all relate to communication between physician and patient.

Potential refractive surgery patients, especially high myopes and high hyperopes, seek options. With a greater understanding of the advantages and limitations of corneal-based refractive surgery, those with high refractive errors find the probability of achieving the convenience of a reduction of the need for corrective lenses less than spectacular.

The phakic intraocular lens has been available outside the United States for the better

part of a decade, and it is reassuring that this panel will have the opportunity to determine if a new option will be available to Americans.

Not surprisingly, I have some concerns. I will leave to others to debate clinical data, and raise only those issue that from a patient perspective are of equal importance.

Pupil Size. Capt. Steven Schallhorn, MD of the United States Navy recently presented a significant performance-based task study of 105 consecutive LASIK subjects to determine what effect preoperative scotopic pupil size has on postoperative night vision.

Dr. Schallhorn's, and subsequent studies, found no direct correlation between scotopic pupil size and reaction-based visual task performance. Although Dr. Schallhorn's study may provide evidence that pupil size alone is a poor predictor of induced night vision problems, I have never heard Dr. Schallhorn say pupil size is not important.

Pupil size may be a poor predictor of

night vision problems, but as any doctor who has prescribed pilocarpine or Alphagan can attest, pupil size is the moderator of night vision problems, when they exist. Although these are two very separate issues, I ask that this panel be mindful of their interrelation.

Furthermore, the corneal-based LASIK procedure is not an intraocular lens. Even further, it is not a phakic intraocular lens. Decades of intraocular lens development have shown the importance of edge design and pupil size in regard to halos, starbursts, and glare in low illumination environments. It seems unreasonable to disregard this body of knowledge, regardless of the conclusions of Dr. Schallhorn's findings.

Should this panel ultimately decide to approve the device presented today, I respectfully ask the panel to consider including in the labeling for both physician and patient that the probability of induced night vision problems when the scotopic pupil is larger than the size of the full optical correction of the device is not easily determined.

I respectfully ask that the patient labeling include a representation of these effects and explanation of probable limitations on the patient, including difficulty driving at night and reading in low illumination environments.

Learning Curve. Today you will have the advantage of evaluating the safety and efficacy of the proposed device when care is provided by what can only be described as some of the best surgeons in the world. I submit that if this device is approved, it will be utilized by doctors who are, shall we say, of somewhat lesser distinction.

With reports of as much as 20% incidence of anterior sub-capsular opacities with the first few patients of other intraocular lenses when implanted by novice surgeons, it appears self evident that proper implantation of an phakic intraocular lens requires not only training, but practical experience.

I have no reason to doubt that the Sponsor will provide significant training in this regard, and I have equally no doubt that this panel will insist on adequate training and proctoring. I believe, however,

it is in the best interest of the patient to be informed of the experience of the prospective surgeon.

Our organization provides a list of 50 Tough Questions For Your Doctor for patients to use as a guide in selecting a refractive surgeon. In our 50 Tough Questions we recommend that a patient seek a doctor who has performed at least 100 refractive procedures of the exact type intend to use on the patient, with the same equipment, and the same refractive error, and significantly more practical experience with similar surgical techniques.

While this panel may find our recommendation of 100 a bit conservative and even restrictive, it does seem reasonable to assume the patient would like to know if he or she is the doctor's first unsupervised phakic intraocular lens patient.

I respectfully request that this panel include in the patient labeling a statement indicating that training and practical experience of the surgeon may be an important factor in the probability of a desirable outcome.

Induced Intraocular Pressure. This panel is much better qualified to determine the safety of the Sponsor's phakic intraocular lens than I, but it appears reasonable to assume that the patient will require periodic evaluation of intraocular pressure during use of the phakic intraocular lens. Who will pay for this care?

Phakic intraocular lens for the convenience of a reduced need for corrective lenses is an elective, arguably cosmetic, procedure. The patient who is making the decision to proceed is making this decision partly based upon cost.

If significantly elevated long-term care were required to maintain good ocular health after phakic intraocular lens implantation, the probable costs for examinations, visual fields, and medication to manage a surgery-induced chronic condition would most probably be an important factor in the patient's decision to elect to have surgery in the first place.

I doubt that it is within the power of this panel to require a doctor to provide long-term cost estimates preoperatively, but it does seem

reasonable that the patient labeling include an indication of the type and frequency of reasonably probable surgery related long-term care.

I'm sure that when presented with this probable treatment plan, the patient will not need the labeling to recognize that these costs should be a part of the decision regarding the relative value of a reduced need for corrective lenses.

Endothelium. There seems to be a lack of clear consensus on the long-term effects of phakic intraocular lens on the quantity and quality of endothelium cells. In the clinical trials, a mandatory evaluation regime underlies the importance of this consideration. The Sponsor is requesting approval for implantation in patients as young as their twenties.

Assuming that the phakic intraocular lens would be utilized until natural cataract development when a person is in his or her sixties, the functional life of a phakic intraocular lens may be as much as 40 years. During this time, the need for regular evaluation of endothelial cell loss seems obvious.

Again, who is going to pay for these costs?

Like long-term care for induced intraocular pressure, it seems reasonable that the patient labeling include some indication of the type and frequency of reasonably probable surgery related long-term care.

Summary. The issues I raise all relate directly to the communication between doctor and patient. All suggestions are for the purpose of promoting that communication. If properly informed of the immediate and long-term issues relating to the Sponsor's phakic intraocular lens, I believe that those patients who elect to have phakic intraocular lens implants will have reasonable expectations and will be able to make the decision that best meets their needs and desires.

Lastly, I do hope that during the course of discussions today I will not hear the term "implantable contact lens". If this is a contact lens, then I've been wearing explantable phakic intraocular lenses when I water ski. Thank you very much for your time.

DR. WEISS: Thank you. I have been told that there is someone in the audience who wanted to

also participate in the open public hearing.

DR. JOHN: Yes.

DR. WEISS: Okay. You have, well, Dr. Grimmett said eight minutes but actually it's now down to seven. If you could identify yourself and any potential conflict.

DR. JOHN: Yes, ma'am. Hi. I'm Maurice John. I'm an ophthalmologist from Louisville, Kentucky/Jeffersonville, Indiana, all in the same metropolitan area. I'm medical monitor for Ophtec. I am not paid by them at all except they paid for my plane fare and my hotel today.

I have no stock which is very good news for Ophtec in that I don't have stock in their company. They would be in trouble. I implanted intraocular lenses starting in 1975. I did radial keratotomy in 1980. In 1993 I had a laser in Sao Paolo, Brazil and we believe the first LASIK was performed with my laser by a colleague of mine in 1993. In 1995 I started doing LASIK in Sao Paolo to get ready for the United States.

In October of 97 I was fortunate enough to

implant the first five ARTISAN lenses in the United States. Prior to that I had gone to Brazil and that summer of '97 implanted a couple of lenses down there. Now I've done 200 plus ARTISAN lenses, the majority of which have been myopic and about 10 percent hyperopic.

Starting out in October '97 I found out that there certainly is a learning curve to implanting this lens which has already been mentioned. It is a short but steep learning curve and there is an advantage to being a good surgeon.

Mr. Hagele's excellent presentation mentioned that he encourages his patients to ask for a surgeon who has done 100 or more cases and that's going to be very, very difficult with an ARTISAN lens because there just aren't many of those people out on the planet. I have a large, busy, refractive surgery practice and I don't know what that number should be but I've been doing it six years and, like I say, I've just done 200 plus of those.

This lens needs space to be put in the eye, there's no doubt about that, but there is

adequate technology to make those measurements to determine if there is adequate space. I would also like to comment on glare. Having done radial keratotomy since 1980 I can assure you that all those patients had starburst and glare and that did not kill radial keratotomy.

Then I've done between five and 10 patients who are in the subset of people who have larger than 6 mm pupils and none of them have glare. I strongly think the reason for that, especially in this population of people who are between -10 and -20 primarily they've had glare, super glare, all their life. So if they get glare from this, it's pretty much peanut glare and then if it's a killer, then this lens can be removed really quite easily.

After that point the problems are primarily if you estimate the anterior chamber depth they are surgeon related and we've seen that time and time again. I introduced this lens in Brazil, as I said, in October of 1997 to my friend Eduardo Martinez who we think is the first guy to do LASIK in North or South America. He was using other phakic IOLs and has

switched to this and now gives paper presentations on it.

I have been to South Africa many times. I go to a meeting over there every two years and I introduced it in 1998 to some of my colleagues there. They also had access to all the phakic IOLs that are available throughout the world.

My colleague, Jan Venter, is up in England now and he is working for a consortium and he gets referred all of the anterior segment surgeries that these LASIK boutiques find. In September of last year he implanted 100 of these lenses. That's how much he believes in their efficacy.

The nice thing about this lens, having done a lot of refractive surgery, when I'm in the office and seeing patients, I walk by and I pull the chart off, I look at it and I see it's an ARTISAN patient and I am so happy because I know that I'm going to be in and out of there quickly and that these patients are going to see well and we have not beat up their cornea trying to do -10.0 or 12.0 diopters on them.

If they see 20/30 they are far happier than a 20/25 LASIK patient. It's amazing. My LASIK patients are always whining. They have some slippage, especially the -7.0, -8.0, -9.0, -10.0 and they are always wanting enhancements even though they are 20/25. These ARTISAN patients have tremendous quality of vision.

It's amazing to me. I just keep reminding myself you're taking the very worse people on the plant, the one or two percent, bottom or top percent, depending on how you want to look at it, and basically pretty much nailing them, knocking a homerun every time up to the plate.

My feeling is that patients should run to this lens and I've had some patients who you say FDA study and you've got to wait three months between eyes and they've gone elsewhere. I've seen a couple of them come back and they said, "I should have listened. I should have come."

The problem we have is, and I had this in 1996, people wanted tried and true RK. They didn't want LASIK. We had the same thing here where 98

percent of these people's friends had LASIK, you know, quick, fast, next day, the American way, and this is a bit of a journey. There are some people who have not had it and it's so unfortunate. I think this lens is wonderful and thank you very much. I hope I beat my seven minutes.

DR. WEISS: By 60 seconds. Thank you.

We will now close the open public hearing and we are going to move on to the open committee session starting with the division update. Dr. Rosenthal.

DR. ROSENTHAL: Thank you, Dr. Weiss. First, let me say that I very much appreciate Donna Lochner coming today because she is theoretically no longer with our division. She has taken a detail with the Division of Cardiovascular Devices as their Deputy Director but has come back to deal with this lens today. We want to wish her all the best of luck on her detail and thank her again for all the hard work she's done for our division and I know she will do a lot of hard work for the Division of Cardiovascular Devices.

Secondly, just as a reminder to all companies, and I'll say this tomorrow as well, but it is important that all companies who are dealing with PMAs with our division schedule a pre-PMA meeting to discuss accountability, stability, safety and efficacy even if they have submitted numerous previous PMAs or PMA supplements. This will help ensure better submission and one that will be less likely to result in a nonfiling decision or result in significant measure deficiencies.

I make these comments because the MDUFMA goals will have to be met in 2005 and the quality of this submission will help us considerably should it be excellent to meet our review goals. Thank you.

DR. WEISS: Thank you. we will now have branch updates by Donna Lochner and Everette Beers.

MS. LOCHNER: Thank you. I am pleased to announce to the panel that Morcher's PMA P010059 was approved by FDA on October 23, 2003. This PMA was for the endocapsular tension ring which is used for capsular bag stabilization in patients with pseudoexfoliation syndrome or other situations of

compromised zonules. You may recall that this PMA was reviewed by the panel in January of 2002.

I'm also pleased to announce that Eyeonics' PMA, formerly C&C Vision, P030002 was approved by FDA on November 14, 2003. This PMA was reviewed by the panel in May of 2003. The PMA was for the CrystaLens Accommodating IOL which is intended for primary implantation in the capsular bag for the visual correction of aphakia in adult patients in whom a cataractous lens has been removed and is intended to provide near, intermediate, and distance vision without spectacles. The CrystaLens provides approximately 1 diopter of monocular accommodation.

Thank you. That concludes my announcements.

DR. WEISS: Thanks, Donna.

DR. BEERS: I'm Everette Beers, Chief of the Diagnostic and Surgical Devices Branch. Since our last update in May of 2003 we have approved three PMAs, P020050 for the WaveLight Allegretto Laser for Myopia and Astigmatism, Ms. Jan Callaway, team leader. The approved indication was for a LASIK correction of

myopia up to -12 diopters with or without astigmatism up to -6 diopters.

We also approved P030008 which, again, was a Wavelight Allegretto laser for Hyperopia and Astigmatism. Let me back up. The WaveLight Myopia was approved October 7, 2003. This one for WaveLight Allegretto for Hyperopia was approved October 10, 2003.

Again, Ms. Jan Callaway was the team leader.

The approved indication for this WaveLight Allegretto Laser was for LASIK correction of Hyperopia up to +6.00 diopters sphere with up to +5 diopters of cylinder with MRSE up to +6 diopters.

On October 10, 2003, we approved P990027/S6 for the Bausch & Lomb Zyoptix, Ms. Daryl Kaufman team leader. The approved indication here was for Wavefront-guided LASIK correction of myopia up to -7 diopters with up to -3 diopters of astigmatism and with MRSE of up to -7.5 diopters.

We've had no staff changes since the last update in October. During 2003 we cleared

approximately 36 510(k)s. This concludes my update.

DR. WEISS: Thank you very much, Everette. That will conclude the branch updates. I just wanted to say for the panel, Donna, that we've all valued all the hard work and the great work you've done and we're going to miss you. Good luck in your new position.

I will now ask the sponsor to come to the podium for presentation of PMA P030028. There will be one hour for the presentation. Each presenter should speak into the mike, identify yourself and your relationship with the sponsor and any potential conflicts.

MR. McCARLEY: Good morning. I'm Rick McCarley, the President and CEO of OPHTEC USA which is based on Boca Raton, Florida. OPHTEC USA is a wholly owned subsidiary of OPHTEC BV based on Groningen, the Netherlands. We are the sponsor of the PMA under review today for the ARTISAN Myopia Lens.

First, I would like to thank the panel for their time in preparing for today's meeting, especially the primary reviewers for their indepth review and comments. I would also like to thank the

FDA team of Dr. Lepri, Dr. Toy, Dr. Gray, and Dr. Lu for their extraordinary effort during the last six months bringing this PMA to panel.

Finally, I would like to thank the audience for their interest and presence at today's meeting to observe the review of the ARTISAN lens. Today's presentation will be made by Dr. Vance Thompson, an ophthalmologist from Sioux Falls, South Dakota, and Dr. Doyle Stulting, Professor of Ophthalmology at Emory University, Atlanta, Georgia.

Dr. Thompson is an investigator in the Artisan lens study but holds no financial interest in the ARTISAN lens or OPHTEC. OPHTEC did pay for Dr. Thompson's travel expenses today.

Dr. Stulting was an investigator in the ARTISAN study and was engaged by OPHTEC following the PMA filing as a consultant. He and Maurice John of Jeffersonville, Indiana/Louisville, Kentucky are medical monitors for this study.

Also today with us is Dr. Camille Budo from Belgium. Dr. Budo is a medical monitor for the ARTISAN lens studies in Europe and is a paid

consultant for OPHTEC BV. He will be available during the day to answer questions related to the ARTISAN lens usage outside the United States.

Finally, Dr. Stan Bentow, the statistician for the PMA, is here to assist as needed. Dr. Bentow is the Department Manager of Biostatistics and Data Management for Advanced Medical Optics. OPHTEC has a business relationship with Advanced Medical Optics for the worldwide distribution of the ARTISAN lens.

With that said, I'll turn the presentation over to Dr. Thompson.

DR. THOMPSON: I'm Dr. Vance Thompson from Sioux Falls, South Dakota. I do not have a financial interest in the ARTISAN lens and my expenses for being here today are being covered by OPHTEC.

It is a sincere honor of mine to present my experience with the ARTISAN Phakic Intraocular Lens implant to the FDA Ophthalmic Devices Panel. After completing a fellowship in refractive surgery with Dr. Dan Durrie in 1990 I entered into private practice in my home state of South Dakota.

I've been integrally involved in multiple

FDA monitored clinical trials as a primary investigator in United States eximer, PTK, PRK, and LASIK clinical trials. I have completed 20 FDA monitored laser and implant clinical trials at my center.

When I was first asked to be a part of the ARTISAN trial, I actually respectfully declined. In 1997 I had a hard time imaging that we would be putting an implant in the eye to correct refractive error. I received a call from an international investigator that I respect who shared with me his positive experience with this implant and asked me to look into this further.

As a result of this call, I chose to go to the Netherlands and study with the inventor of the ARTISAN lens, Professor Jan Worst, to find out more for myself about this lens. I was impressed with it's long track record. I hadn't been real familiar with it at that point.

I basically came away with the feeling that the lens itself had some unique safety features that explain its excellent performance internationally

and with good surgical techniques the outcomes were outstanding.

I saw patients who had had the lens implanted 12 years previously, five years previously, one week post-op, one day post-op. I had a real good experience there and I was impressed enough to then accept the invitation to be a part of the United States clinical trial.

So I came back home and implanted my first ARTISAN lens in September of 1998. I have 74 eyes included in the data being presented today. I was surprised at how quickly I became comfortable implanting this lens and how quiet these eyes looked postoperatively.

A hundred percent of my patients have bee pleased with their outcome and they have all opted to have their fellow eye performed. With continuing enrollment I have performed a total now of 95 ARTISAN lens implants. After having used it, I can't imagine not providing this quality option for my patients in my practice.

This is a single piece PMMA lens for the

correction of myopia. It is elliptical in shape and 8.5 mm in length. It comes in two optic diameters of 5.0 and 6.0 mm. It has a slight anterior vault to create a safety zone between it and the crystalline lens.

The ARTISAN lens is designed for implantation into the anterior chamber of the phakic eye. It is fixated to the mid-peripheral iris by incorporation of a portion of the anterior iris stroma into an opening in the haptic with an instrument specifically designed for this purpose. This process of lens fixation is known as enclavation.

Here is a post-mortem specimen from an 86-year-old who died from an unrelated cause after implantation of an ARTISAN lens six years previously. Note how quiet and undisrupted the posterior uveal pigment appears.

This slit lamp photograph shows an example of the appropriate amount of Iris tissue that should be incorporated into the lens haptic for stable lens fixation. Proper fixation requires incorporation of about 1 mm of iris tissue between the aligned arms of

the haptic. Keep this picture in mind because we are going to be showing you a photograph of an inadequately fixated lens later in this presentation.

An advantage of this lens is the ease with which one can attach it to the iris or detect it from the iris. It can be repositioned during surgery for optimal centration or it can be easily removed by pushing the iris tissue back through the opening in the haptic.

The lens is available in two optic zone sizes, a 6 mm optic in powers of -5 to -15 diopters and a 5 mm optic in powers of -5 to -20 diopters. Here is a Scheimpflug photo showing the healthy separation of the intraocular lens from the cornea and the crystalline lens. This is an 18 diopter lens in a patient with an anterior chamber depth of 3.4 mm.

Since the lens attaches to a relatively immobile peripheral portion of the iris, the pupil can be dilated nicely for an unimpeded view of the retina. The lens is implants through 5.2 or 6.2 mm incision and fixated by incorporating a portion of the mid-peripheral iris into an opening in the haptics with

the enclavation instrument.

The surgery is performed utilizing a cohesive highmolecular weight viscoelastic. A peripheral iridotomomy or iridectomy is required to avoid pupillary block.

Here is an edited video of one of my patients who had an ARTISAN implant and the first step is marking the limbus for the surgical incision and then marks are placed approximately 10 mm apart to locate incision site for the enclavation instrument. Then the initial vertical limbal incision is made and then dissected into clear cornea.

The entry sites for the enclavation instrument are then created, first here on the right and then now on the left. Viscoelastic is instilled with care to avoid overfilling the anterior chamber while providing protection for the corneal endothelium and also the crystalline lens. The anterior chamber is then entered.

If necessary, more viscoelastic can be instilled. The ARTISAN lens is then rinsed. Then it's implanted with Budo forceps, forceps that help to

stabilize the lens. The lens is positioned over the pupil. I like to start with the lens slightly inferior to the pupil since it tends to move superior during lens fixation.

The lens is then enclavated first on the right making sure to incorporate the proper amount of iris tissue, at least 1 mm in width. Here we can see how easy it is to incorporate additional tissue to assure adequate fixation. More viscoelastic can be used to maintain a nice comfortable space between the lens and the endothelium. The left haptic is then enclavated.

At this point in time I would like to put in balance salt solution and then the wound is closed partially. Before the last suture is tied, the remaining viscoelastic is removed from the anterior chamber. Then the last suture tied.

Early designs of this iris fixated lens have been implanted for 25 years with more than 400,000 lenses implanted in aphakic eyes to date. In 1986 a second design known as the Worst-Fechner lens was introduced for implantation into phakic eyes.

However, there was concern that the increased vault of this lens might not provide sufficient clearance from the corneal endothelium.

In 1991 the lens was refined to address these concerns. Note the new profile. This design known as the ARTISAN lens has been used successfully worldwide since 1991. The aphakic iris fixated lens is used all around the world and it is also frequently used as a secondary implant particularly during penetrating keratoplasty.

Stable fixation over time has been shown with normal long-term pupillary function and no iris atrophy. With iris angiogram studies, in this case two months postoperatively, it's been shown that there's no vessel disruption or leakage and normal pupillary function is maintained.

The current ARTISAN lens design has been used for 13 years with over 100,000 myopic, hyperopic, and toric lenses implanted worldwide by more than 5,000 physicians to date. The ARTISAN lens is the most commonly implanted phakic intraocular lens in the world today. It is the lens of choice accounting for

almost two-thirds of implants in markets where multiple phakic IOLs are available.

I'd like to now review the results of European multi-center study of 518 eyes implanted from 1991 to 1999 at nine sites with -5.0 to -20 diopters of myopia utilizing the 5 mm ARTISAN phakic IOL. Three-year follow-up on 249 eyes has been reported in the literature by Budo and coauthors.

Best spectacle corrected visually acuity was better than or equal to 20/40 in 93.9 percent of patients. Uncorrected visual acuity was 20/40 or better in 76.8 percent of patients regardless of postoperative goal. 57.1 percent were within 0.5 diopters of their target refraction and 78.8 percent were within 1 diopter of their target.

Mean endothelial density changes in a subset of 129 eyes were as follows. After six months there was 4.8 percent cell loss; 6 months to one year, 2.4 percent; one year to two years, 1.7 percent; two years to three years 0.7 percent. Notice the relatively low amount of cell loss and stabilization over time.

The results of the European multi-center study demonstrate refractive stability and good predictability. They concluded there was a favorable risk benefit ratio and that efficacy and safety through three years was demonstrated in this study. There are no published reports indicating long-term safety concerns with the current lens design.

Corneal decompensation and glaucoma have not been reported. International experience with complications and secondary surgical intervention parallels that in the U.S. clinical trials. I have a lot of confidence in this lens design which has been in use since 1991. My patients and I both appreciate the fact that it is removable and exchangeable. My personal experience has been excellent.

I find comfort in the long-term performance demonstrated in the European study and the published literature. The two-thirds market share for phakic IOLs means a lot to me when the majority of surgeons in the world who have their choice of which phakic IOL to implant choose the ARTISAN lens.

I consider this a quality surgical option

for high myopes and I also consider this a quality surgical option for low myopes who are not good candidates for other refractive procedures. I am enthusiastic about the results from this lens and I look forward to its approval. Thank you very much for your attention.

I would like to now turn the podium over to Dr. Doyle Stulting who will review the results of the United States clinical trial.

DR. STULTING: Good morning members of the Ophthalmic Devices Panel and the FDA. I'm Doyle Stulting, Professor of Ophthalmology at Emory University. I'm one of the medical monitors of the ARTISAN Phase III clinical study and a paid consultant to OPHTEC. It will be my pleasure to present the results of the U.S. clinical investigation of the ARTISAN myopia lens for the correction of high myopia.

This was an open-label, noncomparative study of patients with 4.6 to 22 diopters of myopia. The lens was available in one diopter power increments and two physical designs. The 5 mm optic was available in powers from -5 to -20 diopters and the 6

mm optic was available in powers from -5 to -15. There were eight postoperative visits.

Note, however, that the study was initially planned to spend two years and later extended to three years. The results were obtained from all implanted lenses by all investigators. Specifically, investigators for this study did not receive training outside of the U.S. or experience outside of the U.S. before they began to participate in the clinical trial.

To be included in the original study subjects had to be 21 to 50 years old with a stable manifest refraction or refractive cylinder of 2 diopters or less, an anterior chamber depth of 3.2 mm or more, and an endothelial cell density of 2,000 or more per millimeter square. The low-light pupil size had to be 4.5 mm or less because only the 5 mm optic was available at the time of study initiation. There can be no ocular disease or abnormality that would affect safety.

The FDA granted a number of protocol waivers to allow implantation in patients who did not

meet all of these criteria until the original protocol was amended with expansion inclusion criteria in November of 2000.

These expanded inclusion criteria allowed enrollment of eyes with clinically insignificant and stable peripheral lens opacities, astigmatism of 2.5 diopters or more, anterior chamber depths of less than 3.2 mm, age over 50, pupil size greater than the size of the optic, best spectacle corrected acuity of less than 20/40, and implantation of lenses that would not completely correct the refractive error.

Outcome measures included uncorrected visual acuity, best spectacle corrected acuity manifest in psychoplegic refraction, contrast sensitivity, intraocular pressure, endothelial cell density, and slit lamp observations.

At the time the protocol was developed, cataract formation was not identified as a significant risk because of a six-year history of implantation internationally without cataract induction, and the position of the implant well clear of the crystalline lens. Thus, the approved protocol required only

clinical grading of cataracts rather than standardized grading of lens opacities.

In 1997 when the study was initiated a variety of instrumentation was permitted for obtaining specular images and only one image was required for each eye at each visit. As the available technologies and the knowledge advanced, the sponsor changed investigational procedures consistent with FDA, ANSI and ISO discussions in developing guidelines.

This led to a recommendation from the sponsor that sites use only the Konan non-contact specular microscope and obtain three satisfactory images for analysis for each eye at each visit.

Six hundred and 84 subjects were enrolled. There were 662 subjects in the primary study 478 of which were implanted bilaterally. Twenty-two were implanted for compassionate use. Enrollment is ongoing.

The PMA defines several groups for analysis. For this presentation, most safety analyses were based on all implanted eyes while efficacy studies were based on first eyes. Accountability was adequate and the study is ongoing. Two hundred and 32

first eyes have completed three years of follow up and 357 subjects continue to be followed.

This PMA filing is based on 386 eyes which were followed for three years. At three years 62.4 percent of eligible eyes have completed their exams with a large portion of the remainder still to be seen. In judging these numbers the sponsor feels that it is important to be mindful of the fact that this was originally designed and powered as a two-year study. Subjects were recruited with this understanding and some of them elected not to return for their three-year visit.

The number of discontinued subjects was low with only eight percent lost to follow-up. Demographics were not unusual for refractive surgery population with a mean age of 39.6 years. The mean preoperative spherical equivalent refractive error was significantly higher than the mean error of patients seeking refractive surgery in this country today. It was -12.3 diopters. The range was 4.6 to 21.9 diopters.

As we move forward it is important to

remember that many of the subjects in this study are high myopes who have no other alternatives for refractive surgery. This population is also at increased risk for undesirable outcomes such as cataracts and retinal detachment. The mean lens power was -12.6 diopters ranging from 5 to 20 diopters.

Let's look at the safety of the lens. One hundred percent of first eyes has best spectacle corrected acuities of 20/40 or better at two and three years after surgery. As you can see from this slide, best spectacle corrected acuity was better at one, two, and three years postoperatively than it was preoperatively.

At three years 49 percent of eyes gained best spectacle corrected acuity while only 6.2 percent lost best spectacle corrected acuity. Two eyes lost two lines of best spectacle corrected acuity. No pathology was reported in either of these eyes so the loss is believed to be due to measurement variability.

I want to pause with this slide because it shows something that previously approved forms of refractive surgery do not, improvement in best

spectacle corrected acuity after surgery. Indeed, the fact that only two eyes in this study lost vision is a remarkable result in view of the degree of preoperative myopia and the age of the subject population.

The incision size --

(Whereupon, off the record from 10:14 a.m. to 10:19 a.m.)

DR. STULTING: -- possible dislocation. There were 20 of these. The majority of these procedures were performed at a single investigational site. Most of the procedures were preventative measures taken to avoid possible dislocation. The sponsor advocates comprehensive training of surgeons to minimize similar events after approval.

This graph shows the number of secondary surgical events as a function of the number of implants performed by the investigators in the clinical trial. It is clear that the majority of secondary surgical interventions occurred during the early surgical experience.

Approximately 50 percent of the events

occurred among the first 10 subjects implanted. A disproportionate number occurred at one site and the majority was due to improper lens fixation. These procedures include both preventable and therapeutic interventions.

These data show that there is a learning curve for some of the skills required for successful implantation of the ARTISAN lens. Retinal detachment occurred in six eyes during the observation period. This represents an incidence of 0.3 percent per eye per year in a population of eyes with myopia between 11.5 and 18.6 diopters. This rate is comparable to reported rates of retinal detachments in the literature in high myopes.

This slide shows the incidence of lens opacities in the study. Most were not visually significant or lens related. Only one eye lost two lines of vision to 20/30. Most lens opacities were nuclear which would not be expected to be related to an implanted lens. Only a very few were anterior or subcapsular opacities which would be expected if they were intraocular lens related trauma to the

crystalline lens.

This slide summarizes significant lens opacities requiring cataract extraction during the study. One occurred after removal of viscoelastic and intraocular lens implant for high intraocular pressure.

A second was in a 50-year-old with a family history of cataracts. The third was in a 56-year-old man with a preoperative lens opacity and a family history of cataracts. The sponsor does not believe that the incidence of cataract in the study population is unexpected given the age and refractive error of the study cohort.

These are the visual outcomes in eyes that underwent secondary surgical intervention. Even in this group more eyes gained best spectacle corrected acuity than lost best spectacle corrected acuity compared to the preoperative value. The 3.7 percent represents two eyes that lost two or more lines of best spectacle corrected acuity.

Here are the details pertaining to these two eyes. One was due to a retinal detachment and a

subsequent macular hole 20/70. The other was due to posterior capsule or haze following cataract extraction and intraocular lens implantation. After YAG capsulotomy this eye had a best corrected acuity of 20/30.

The Agency requested data on adverse events that have occurred since submission of the PMA. There were two of these. One was a cataract extraction that was necessitated by repair of a retinal detachment with trauma to the crystalline lens.

The second was reattachment of a lens that was dislocated during a boxing match. I'm not sure whether he won or lost. The most recent visual acuities in these two eyes were 20/30 and 20/40. Let us discuss endothelial cell density in greater detail. At the time of initiation of the study in 1977 the protocol allowed a variety of instrumentation and required acquisition of only one image per eye per visit.

As technology improved, the protocol was changed. However, it was impossible to acquire old

data according to the improved protocol retrospectively. The data presented to the FDA are consistent with the guidance provided to industry by the Agency and the Ophthalmic Devices Panel at the time the study was designed.

This slide shows the results of endothelial cell counts in the original PMA. Although there was not significant reduction in endothelial cell density, the standard deviations of the measurements were relatively large ranging from 17 to 25 percent.

The data set that was reported in the original PMA was derived from one to three images per eye per visit using a variety of instrumentation. The images were analyzed by various site personnel. Because of the variability there was not good statistical power to rule out significant changes in endothelial cell density.

Review of the raw data led to the conclusion that analysis of the specular images could be improved. The sponsor elected to recount available high quality images after consulting with FDA and

experts in the field. Data from 12 sites were chosen because they used the Konan specular microscopes. This instrument is now the accepted standard for the most accurate determination of endothelial cell density.

One reading center was employed for consistency. Only the best quality image was analyzed per eye per visit. There were a total of 353 eyes of 215 subjects producing a consistent cohort of 57 subjects with data at all time points throughout three years. The average number of cells analyzed per image was 109.

Here we see the mean endothelial cell density in all recounted subjects and the consistent cohort. Both showed a slight reduction which would be expected even in the absence of intraocular lens implantation.

The equivalent yearly rate of cell loss ranged from 0.72 percent to 1.59 percent throughout the study when all recounted eyes were analyzed. Note the reduction in the standard deviations in the recount analysis.

In the consistent cohort yearly endothelial cell density loss rates range from 0.71 percent to 1.27 percent. This slide shows percent change for each observation period. Changes between consecutive periods are not statistically different. Similar results were obtained in the consistent cohort.

One site exhibited an endothelial cell loss for the two to three-year period of 4.95 percent which was significantly lower than any of the other sites. The sponsor was recently notified that the site had staffing changes, problems with calibration of the specular microscope, and that the microscope required servicing during this period. The results from this site may not be poolable.

Removing this site from the analysis decreases the loss for the two to three-year period from 2.37 to 1.68 percent. The accuracy and precision of specular microscopy with the Konan noncontact specular microscope is documented in the publication by Nichols and coworkers in which 25 normal subjects were examined on two occasions by two examiners. The

mean instrument error was 1.7 percent with a confidence interval from -13 to +16 percent.

The important point to be learned from this published paper is that a cell loss reading of 10 percent is within the confidence interval of measurement error and 13 percent of eyes would be expected to have a 10 percent change or more even if no real change existed.

Here we see the yearly change in endothelial cell density and the two to three-year periodic rate. These are not significantly different from guidance. The average cell loss over time was about 50 cells per millimeter square per year or 1.72 percent per year. The projected mean cell count is about 1,300 30 years after implantation.

There was no change in the percent of hexagonal cells and the coefficient of variation after surgery. These data support the conclusion that the implanted lens does not stress the endothelium because a reduction in hexagonality and an increase in coefficient of variation are hallmarks of chronic endothelial stress such as we see with long-term

contact lens wearers.

When the endothelial cell density was analyzed, there was no consistent statistically significant association with gender, age, lens model, anterior chamber depth, or preoperative spherical equivalent manifest refraction.

We conclude that the endothelial cell density loss after implantation of the ARTISAN lens is within the acceptable range. There are no statistically significant differences in loss rates between consecutive periods. The loss that was recorded is within measurement error.

In summary, the ARTISAN lens has a superb safety profile with excellent best corrected acuity. Most secondary surgical procedures were due to inadequate lens fixation and could be prevented in the future by surgeon training and proper attention to surgical techniques.

Even when secondary surgical intervention was necessary, best spectacle corrected acuity was maintained. Lens opacities were generally mild, not visually significant, and unrelated to the intraocular

lens. The endothelial cell loss was within the acceptable range.

Let's take a look at efficacy. Ninety-two percent of first eyes targeted for emmetropia with preoperative best spectacle corrected acuities of 20/20 had 20/40 or better visual acuities at three years postoperatively. Fifty percent of these eyes had 20/20 or better visual acuity postoperatively.

This slide gives the details of eyes with uncorrected acuities less than 20/40 at three years after surgery. Most or attributable to residual refractive error, usually residual astigmatism. The sponsor believes that the reported uncorrected acuity of 20/70 in one subject was due to a testing or reported error since this subject had a best spectacle corrected acuity of 20/20 and a minimal refractive error.

Remember that only one diopter lens power increments were available in the study. Subjects were included with more than 2.5 diopters of astigmatism without astigmatic correction. We expect uncorrected acuity to increase after approval because of the

availability of half diopter power increments and the use of astigmatic corrective procedures when necessary.

As we improve refractive surgical techniques, the comparison of best postoperative uncorrected acuity to preoperative best spectacle corrected acuity is becoming a more discriminating outcome measure. In this study a remarkable 51 percent of eyes targeted for emmetropia had a postoperative uncorrected acuity better than or equal to the preoperative best spectacle corrected acuity.

71.7 percent of eyes were within a half a diopter the target refraction and 94.7 percent were within one diopter of target. Postoperative refractions were remarkable stable with less than a 10th of a diopter change between six months and one year and between two and three years.

The vast majority of subjects were pleased with the quality of their vision, satisfied with their outcomes, and would recommend the procedure to their friends. Visual aberration such as glare, starbursts, and halos were noted in about the same number of

subjects after surgery as before surgery.

The majority of subjects had no change in their reported visual symptoms after surgery compared to preoperatively. The only reported symptom that was more frequent postoperatively than preoperatively was halos. We may see the reason for that in subsequent slides.

We look for correlation between visual symptoms and parameters relating to the lens or the eyes in this study. There was no significant correlation of visual symptoms with the relationship between the lens optic and mesopic pupil size, lens power or refractive cylinder except for halos in refractive cylinder which is probably an explanation for the increase in halos postoperatively.

After approval the sponsor believes that postoperative symptoms due to residual refractive error will be reduced because of the availability of half-diopter lens power increments and the use of additional surgical procedures to treat residual astigmatism.

A 20 diopter myope with a 2.5 diopter

corneal astigmatism preoperatively who has 20/40 uncorrected acuity after implantation and residual nighttime glare may be ecstatic about his or her surgical result but raise concern among panel members because of the presence of nondebilitating visual symptoms at night postoperatively.

Contrast sensitivity was investigated in a substudy involving 31 subjects. Under photopic conditions without glare, contrast sensitivity was better postoperatively than preoperatively. There were similar results with glare reaching statistical significance at four out of five of the measured points, again with better performance after surgery than before.

Under mesopic conditions without glare contrast sensitivity was the same postoperatively as it was preoperatively. The same results are seen under mesopic conditions with glare.

In conclusion, there was no decrease in contrast sensitivity after implantation of the phakic ARTISAN lens. Statistically significant differences where present usually show better contrast sensitivity

postoperatively than preoperatively, very different than currently approved refractive surgical procedures.

In summary, the ARTISAN lens offers excellent uncorrected visual acuity, excellent predictability, good stability of refraction, contrast sensitivity that is unchanged or improved, and high subjective satisfaction rates. The sponsor proposes that the ARTISAN lens be labeled for the correction of myopia with lenses from between five and 20 diopters.

Although preoperative refractive cylinder greater than 2.5 diopters was an exclusion criterion for the study, the sponsor does not believe that it should be a contraindication for the use of the ARTISAN lens after approval because residual astigmatism can be managed by the placement of the surgical incision site and other techniques.

We suggest that the lens optic size be greater than the mesopic pupil size when possible. However, we note that no correlation was found between the disparity between optic size and pupil size and visual symptoms at night. Because subjects in the

study with preoperative pathologies did not have different results than those without pathology, the sponsor proposes that preoperative pathologies not necessarily preclude the use of the ARTISAN lens.

Endothelial cell density minimums for each age group would be acceptable as a precautionary measure at the discretion of the panel and the FDA. Our experience with inadequate iris fixation primarily at one site emphasizes the need for appropriate physician training in the use of this lens.

The sponsor proposes that the lens be made available only to surgeons who have undergone appropriate training including didactic instruction, supervised wet lab training, observation of live surgery, and supervised initial procedures.

There are a number of benefits of the ARTISAN lens compared to other refractive surgical techniques. The ARTISAN provides excellent refractive outcomes. As opposed to other commonly used refractive surgical techniques, the ARTISAN lens leaves contrast sensitivity unchanged or improved.

There is a good safety profile with few

complications most of which can be avoided by adequate training and surgical technique and attention to detail during the surgical procedure. Endothelial cell loss was within the expected range and there was very high patient satisfaction.

The lens is exchangeable and removable with good outcomes. It avoids the potential complications of corneal surgery such as scarring, complications of flap preparation, and irregular astigmatism. It provides an effective treatment for myopes, especially those who are not candidates for other refractive procedures.

The sponsor asks that the ARTISAN phakic IOL be recommended for approval. Thank you.

DR. WEISS: Seeing that concludes the sponsor's presentation, I would like to thank the sponsor for the clear presentation and we are going to break for 10 minutes. I would request that everyone be back here promptly in 10-minutes time.

(Whereupon, at 10:40 a.m. off the record until 10:56 a.m.)

DR. WEISS: We are going to begin with

questions from the panel to the sponsor so I will ask the sponsor if they could take a seat up front. Okay. I'm going to be changing the format a little bit for the edification of the panel today and what I'm going to be doing is going around the table and asking you what questions you might have for sponsor in the attempt to maximize our time.

I have one question. You mentioned that there were three cases where the pupil size was larger than the optic size. Did those patients have any halo or glare or visual symptoms associated with that?

MR. McCARLEY: Yes, they did and, in fact, there were three patients who had their lenses removed that had the optic size larger than the pupil -- sorry,, the pupil larger than the optic size. But there were many more patients in the study that had larger pupils than the optic.

DR. WEISS: I think I'm confused then. I heard from Dr. Stulting that he identified particularly three patients that had pupil size larger than optic. But from what I'm hearing right now, there were more than three patients?

MR. McCARLEY: That's correct. There were three patients. The slide identifies three patients who had lens removal or secondary surgical procedures as a result of that.

DR. WEISS: Okay. So then there were three patients with lens removal because the pupil size was larger than the optic size and they were symptomatic.

MR. McCARLEY: That's correct.

DR. WEISS: But how many patients had pupil size larger than optic size?

MR. McCARLEY: I'll have to pull the PMA.

DR. WEISS: So you can get that?

MR. McCARLEY: Yes, we can get that.

DR. WEISS: The other question on that, because of glare symptoms at night in relation to one of the people who gave a comment at the open public hearing, were any of the patients needed to be on Alphagan at night?

MR. McCARLEY: Not that we're of specifically for that purpose, no.

DR. WEISS: Okay. So we're going to go

around. Glenda, did you have any comments or questions?

MS. SUCH: Two questions small in nature. One is what was the youngest age you actually had in the study group?

MR. McCARLEY: It was 21, I believe.

MS. SUCH: That's what I thought I heard. I can't remember the second question so I guess that's it.

DR. WEISS: Well, we can get back to you.

Mr. Balo.

MR. BALO: I don't have any questions.

DR. WEISS: Dr. Schein.

DR. SCHEIN: I have comments coming up later but only one question now. I'm wondering about data from other sources that could be brought to bear?

MS. THORNTON: Oliver would you --

DR. SCHEIN: My mike is too far away. I'm interested in data from other sources on the device that might be useful. What I've heard so far relates to this long-term series of 19 patients in Europe. It's a consistent cohort but it's a very, very small

group.

Dr. Stulting mentioned a publication out of Europe recently but that group reported only 50 percent of the patients that they started with. Are there any data sources available with 100, 200, 300 patients with three, four, five-year follow-up that we can examine?

MR. McCARLEY: Not that we are aware of. Obviously there have been recent publications that have started to come out where more people became involved, especially in Europe in the mid-'90s who have longer term data now.

Dr. Mihai Pop from Canada also has some data that I believe will be produced in the next month or two in one of the major journals. But as far as answering your question, I don't think anyone has done a large study of endothelial cell count for a long term.

DR. SCHEIN: I needn't even be restricted to endothelial cell count. Something would disconnect if there are 100,000 implants that have been done and there is essentially no data externally with high

levels of follow-up.

DR. STULTING: This is Doyle Stulting. I can address that a little bit. The European study was 518 eyes with a three-year follow-up on 249 eyes. That's Dr. Budo's paper. I think the number that you were referring to is the endothelial cell density study and that was 129 eyes followed for three years.

There probably aren't any rigorously followed series of eyes out there in the literature giving us two or three-year follow-up with the accountability that we would like to see because of the nature of the refractive surgery population. What we do know is the number of implants that have been used and the lack of reports of significant long-term complications so that gives me at least a little bit of comfort knowing that there are so many lenses out there in eyes and, yet, there aren't reports of problems with these lenses long term.

DR. SCHEIN: In Europe is there mandatory reporting with explantation?

MR. McCARLEY: Yes. In fact, it's required as part of the CE process. In Europe they do

require you to report adverse events -- all adverse events.

DR. ROSENTHAL: May I just add that as part of the PMA process it's the sponsor's obligation to submit all data that's been published that they know of in the literature and not in the literature about the device. The FDA does receive everything that is supposed to be -- that is out there. It's supposed to be submitted with the application.

DR. WEISS: Dr. Macsai has a question on that point.

DR. MACSAI: I have a question for Dr. Rosenthal. Does that include CE data? Do you share with CE and does CE share with the FDA?

DR. ROSENTHAL: The data we are supposed to receive is the data that the company submits that they know is in the public domain. CE data may not be in the public domain. Many of the countries within the European community consider much of the adverse event data to be confidential.

I think with Britain we do have some sort of mutual agreement that when there are serious

problems with the device, we are notified and, likewise, they are notified when we have serious problems. But generally there is not a worldwide sharing of data relating to post-market problems with devices.

DR. WEISS: We're going to go on to Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: Thank you. I just have a couple of questions about the endothelial cell count data that was presented in the PMA. The first is that there were 12 sites that contributed data to the final analysis. I'm wondering if you can tell us whether you've analyzed data to determine how those sites compared to the sites that did not contribute data to that analysis other than not having the Konan microscope, things like case mix, provider experience, anything like that?

MR. McCARLEY: The Konan machine provides a relatively good image that is standard. And they also provide a separate software that actually provides a way to read images in the standardized way. It was out choice based upon the recommendations of

the experts, some of which have testified in front of this panel, which machine is likely to give you consistent good readings. Not favorable readings but to be able to read it at all. In fact, we utilized exactly the same machines as Dr. Edelhauser, for instance, and some of the others around the country that actually do endothelial cell counts.

DR. BANDEEN-ROCHE: But what I'm getting at is that only 10 of the U.S. sites use that microscope and how might those sites have been different than the others?

DR. STULTING: Maybe I could ask Dr. Bentow for a little bit of help. Did you look at the baseline for the two sites?

DR. WEISS: You can identify yourself.

DR. STULTING: For the groups of sites that were included in the endothelial cell versus those that were not.

DR. BENTOW: Yes, this is Stan Bentow with AMO. We didn't look at a comparison with the previous data set because we went with only the Konan pictures that we used in the latter one, although we did look

at site comparison and analysis for that data set, the recounted data set.

DR. SCHEIN: Did you make a comparison --

DR. WEISS: Dr. Schein, can you identify yourself?

DR. SCHEIN: Right. This is Oliver Schein. Did you make comparisons within those centers that were using the Konan scope as to who is in versus who is out? By that, I mean you have images on a very small proportion of the total images that were generated even at the sites that used that technology. It would be useful to know rates of adverse events in versus out, baseline cell counts, age, etc. Do you have those to show us?

DR. BENTOW: We can look at that and see if we can bring that up.

DR. WEISS: Thank you. Dr. Bandeen-Roche, if you have no other questions.

DR. BANDEEN-ROCHE: I have one more question that actually goes to that. I believe I read in the updated part of the PMA that images with the number of cells counted less than 70 per reevaluated

and if it was felt that they weren't of good quality, they were not eliminated. This seems potentially biasing to me. It seems like that could well undercut the rate of loss by excluding the images with the low cell counts. I wanted to give you a chance to respond in case I'm just not understanding.

DR. STULTING: I understand what you're asking. I can tell you that the site that we mentioned that had the high rate of secondary surgical procedures and what not was one of the sites that was included in the recount data.

DR. WEISS: Dr. McMahon.

DR. McMAHON: Tim McMahon. I have two questions. The first continues along the line of endothelial cell counts. Were test and retest analysis done by individual sites and were there any variances in the 95 percent confidence intervals amongst those sites?

DR. STULTING: No, looking at test/retest for a single site was not part of the protocol. Once again, the protocol was developed back in 1997 when these kinds of questions were really not at the top of

our minds and we weren't looking for a technology that gave us the ability to discriminate a .6 percent loss from a 1.6 percent loss over a period of a year. Those parts of protocol that we might want to design today for a very scientifically rigid investigation were not part of the investigation that we are reporting today.

DR. WEISS: We do not have the amount of time to have the sponsor coming up to the podium at this point so we are going to have to continue along with these questions.

Dr. Bradley. Oh, I'm sorry. Dr. McMahon.

DR. McMAHON: This is my second question and it's in a completely different area. I was troubled by the number and percentage of protocol deviations. I think it was as high as over 20 percent and I'm kind of concerned as to what the rationale for that was. There are a couple of cases identified.

In particular, initially three comments or comments about three patients with pupils larger than the optic and now new statements saying that there's more than that. There's protocol instructions and

inclusion/exclusion that prohibits that and what is the justification for all these?

DR. STULTING: We tried to address this question in the presentation since it was raised in some of the comments from the panel that were forwarded to the sponsor. The original protocol that was designed in 1997 had exclusion and inclusion criteria.

For example, for astigmatic error that was present before surgery patients who were high myopes who had no other choice of refractive procedures requested ARTISAN implantation. Their surgeons requested it from the sponsor. The sponsor requested protocol deviations for the FDA for use compassionately in these patients and it was granted.

As the time went by eventually in the year of 2000 the FDA and the sponsor expanded the protocol inclusion criteria so that patients with anterior chamber depths less than 3.2 mm, pupil sizes greater than the optic size and high astigmatism could be implanted with informed consent and so these patients were later included in the protocol and that's how

they got in there.

It wasn't because investigators enroll people that they shouldn't enroll. It was because the indications were expanded with informed consent, knowledge of the Agency, and a decision on the part of the sponsor.

DR. McMAHON: So the FDA okayed each one of these?

MR. McCARLEY: This is Rick McCarley. Initially we received very few requests for protocol deviations in our study. As time progressed and we believe as surgeons became more comfortable with the procedure, the surgical technique itself, they started to receive more patients and see more patients that they believe could be assisted by it but, in fact, at the same would not be compromised.

We started to get more and more requests for protocol deviations. We worked with the FDA, the Agency, to create an arm, a substudy. It's called Protocol Deviation Substudy. All of the criteria except a certain list of items that Dr. Stulting mentioned were included. These patients signed an

additional informed consent on top of the normal informed consent for the study.

DR. WEISS: I would just follow through and I'm just repeating what you said. What percentage of the protocol deviations were granted with the update approval and what percent were not?

MR. McCARLEY: All of them were --

DR. WEISS: A hundred percent.

MR. McCARLEY: A hundred percent were known by the FDA or approved by the FDA. We either gained approval from the FDA on a one-by-one basis before the substudy started and after the substudy started they were approved by the institutional review boards. The patient included them in the normal enrollment.

DR. WEISS: So 100 percent were approved by the FDA before they had the surgery.

MR. McCARLEY: Correct.

DR. WEISS: Dr. Bradley.

DR. BRADLEY: The sponsor emphasized that the procedure led to improved visual acuity and improved contrasensitivity. I wondered if the sponsor

had evaluated the relative importance of image magnification and image quality on these changes in acuity in contrasensitivity?

DR. STULTING: We recognize image magnification and we recognize the potential improvement in image quality because of the placement of the corrective lens but nothing was designed in the protocol to look at these things specifically, objectively, and scientifically other than the collection of data that you have in front of you.

DR. WEISS: Dr. Macsai.

DR. MACSAI: I just want to first follow up on your comment, Dr. Stulting. This increased visual acuity that was shown on the slides during your presentation is accountable due to the magnification of the IOL. Correct?

DR. STULTING: Some of it is. That's correct.

DR. MACSAI: And in your contrast sensitivity studies, how was the contrast sensitivity measured preoperatively as for point of comparison? Was it measured in spectacles?

DR. STULTING: Yes.

DR. MACSAI: So what did you expect if someone is -12 in their spectacles that their contrast sensitivity would be decreased versus that with an intraocular lens?

DR. STULTING: Are you asking --

DR. MACSAI: Would you expect these results from placement of an intraocular lens?

DR. STULTING: I think I would and I think I would be pleased.

DR. MACSAI: It's because of the difference between the spectacle and the movement of the lens inside the eye and the lack of changes in refractive index.

DR. STULTING: That's probably correct.

DR. MACSAI: Okay.

DR. WEISS: Dr. Grimmett.

DR. GRIMMETT: Dr. Michael Grimmett. My first question was already addressed by Dr. Macsai and Bradley regarding magnification. The second point I wanted to make was that Dr. Stulting showed a slide regarding the lack of change and hexagonality and

coefficient of variation. This was a fairly young cohort of patients, I think, ranging from 21 to 50 something with an average range in the 30s, I believe.

As Dr. Edelhauser confirmed on our October meeting when I asked him the same question, a young cohort can have a very robust endothelium and really mask the morphemetric data so it's stress factors that we all think of regarding these changes which may manifest in an older subgroup can be completely hidden in populations this young. I just wanted to point out that fact when we considered the endothelial data. That's all I have.

DR. WEISS: I had one other question in terms of trauma dislocating this lens. Would you then advise patients who were in careers such as boxing or hockey or whatever that that would be a contraindication to having the lens? Basketball depending on how you play it?

DR. STULTING: I think that's a reasonable suggestion.

DR. WEISS: Dr. Mathers.

DR. MATHERS: Dr. Bill Mathers. I seem to

feel a sort of disparity between the study -- the mean of the study group and that which the sponsor is asking permission to include later. The mean here was 39 years of age and -12 refraction. It might be that this is actually the group that you feel that this lens is the most advantageous for and has the greatest impact.

In fact, one could say that Dr. Stulting's comment that there is no other choice for some of these people may be a factor but you are requesting permission for patients down to 20 and a refractive error that is much lower than this. How do you -- help me with feeling how these two groups actually compare and the justification for using it in a larger group.

DR. STULTING: The profile of the refractive -- of the patient population in this study pretty much parallels the clinical practices and the refractive populations that are part of publications for refractive procedure in the literature so far. The mean age, in fact, for all of these is pretty consistent at 39.

As a consumer of this technology, I would like to have it available to me to use in circumstances for I feel it is appropriate. There may be a relatively young patient who has a relatively thin cornea who would be an appropriate candidate for it based on parameters other than age.

I would like to have it in my armamentarium so that I can offer it to that person. I think that the selection of procedures for refractive surgery has to be based on many more things than the refractive error and the age.

DR. WEISS: Dr. Casey.

DR. CASEY: Richard Casey. Dr. Thompson, you showed a slide and you made the comment that there was no iris vessel disfunction or leakage in patients in this study, but the title of the slide was an angiogram two months post-op with an aphakic IOL. My question is was there a systematic evaluation by angiogram of patients in this study?

DR. THOMPSON: No. We didn't do angiography in this study. We were basically showing that because some of the disadvantages of other

implants in the past than chronic cell and inflair from vessel leakage and we wanted to show the integrity of the blood/aqueous barrier for this lens.

DR. CASEY: My question was related to there was a small number of minority patients in this study and we know that there are patients that have different -- the iris is of different thickness and different vascular density and so issues of inflammation could be important in different subpopulations. If it wasn't done, it wasn't done.

My second question is can you tell us anything about the endothelial cell loss in those patients who required a second surgical procedure and were they followed after the second procedure to determine if there was any accelerated rate of attrition of endothelial cells?

DR. STULTING: We can try to get those numbers specifically for you after lunch but I can reiterate the point that I made before and that is that the site that had most of the secondary surgical procedures was one of the sites that was in the recounted endothelium cohort so we have a good bit of

information on those patients in particular. Let me make a note of that and we'll try to get the data. The specific question is endothelial cell counts on people with secondary procedures.

DR. CASEY: Yes.

DR. WEISS: Dr. Coleman.

DR. COLEMAN: Yes, this is Anne Coleman. I had a question regarding your exclusion criteria for patients with glaucoma. How is that determined for those individuals to be excluded? Was it by visual field and optic nerve evaluation, or was that by clinical judgment?

DR. STULTING: I'm afraid we didn't probably use the strict criteria that a good glaucoma specialist would request. It was based on clinical diagnosis and the use of medications.

DR. COLEMAN: And then --

DR. STULTING: A refractive surgeon's diagnosis, I guess.

DR. COLEMAN: And then at one, two, and three years how many of the patients were on chronic glaucoma medications for maintenance of intraocular

pressure?

DR. STULTING: Ten out of 1,147.

DR. COLEMAN: Thank you.

DR. WEISS: Dr. Van Meter.

DR. VAN METER: Woody Van Meter. A couple of questions for Dr. Stulting. Early on in your presentation you were talking about training and mentioned that all investigators were trained for this study in the United States. Is that correct?

DR. STULTING: That's correct.

DR. VAN METER: We had anecdotal evidence from Dr. John about multiple procedures done in South America and South Africa and those patients were not part of this study. Dr. Grimmett has already covered my concerns about the statistical legitimacy of the endothelial data and I guess we can talk about that later.

On slide No. 60 that you showed, there was reference to a 56-year-old with a preexisting cataract who had a family history of cataracts who had an ARTISAN lens implanted. That seems to be a little bit outside the box.

MR. McCARLEY: Rich McCarley. There were actually two patients in the study that had a family history of cataracts but that wasn't found out until after the patient had actually received the implant. In one case I'm very familiar with, the surgeon implanted the first eye and six months later was getting ready to implant the second eye and noticed the cataract in the first eye. Upon further interview with the patient found out, in fact, it was familial.

DR. VAN METER: Well, I'm not concerned about the family history as much as I am the 56-year-old who was already presbyopic and nearing cataract age anyway must have had it noticed beforehand since it was called a preexisting cataract.

MR. McCARLEY: It wasn't and the patient chose the surgery. The surgeon felt that there was a possibility that it wasn't likely to develop.

DR. VAN METER: Okay. Thank you.

Dr. Stulting, slide 80 you mentioned that proper training will reduce the incidence of complications. Since we have data here from the finest surgeons in the world doing these cases, how

are you going to alter the training technique that is listed in slide 102 to reduce complications when mere mortals try to do the surgery?

Slide 102 lists a number of objectives from training, most of which I believe are already, as I peripherally understand it, part of the ARTISAN training program. Can you tell me how you are going to change the training?

DR. STULTING: I'm not exactly sure that I understood the question. Could you repeat it?

DR. VAN METER: Yes, sir. On slide 70 you mentioned that proper training will reduce the incidence of complications. Slide 102 you list the training proposal but, as I understand it, this training proposal is pretty much how training has existed for ARTISAN investigators.

DR. STULTING: I don't think -- there is no question that this surgery is different from what ophthalmologists are used to performing as you could see from the video clip. There is bimanual dexterity that is involved. It's a little bit greater than the bimanual dexterity that we are used to having in other